REMARKS

Claims 11 and 19-23 are pending.

Claims 1-10 and 12-18 have been canceled without prejudice to filing a continuing application claiming any deleted subject matter.

New claims 22 and 23 have been added. Claims 11, 19 and 20 have been amended without prejudice to filing a continuing application claiming any deleted subject matter. Support for the new claims and amendments are found in the application as originally filed. Pharmaceutically acceptable salts are found at ¶¶[0078, 0114 and 0115]. Pharmaceutical compositions and pharmaceutically acceptable carriers are found at ¶¶[0077-0085]. The compounds covered in claim 23 are supported by compounds 18 and 19 shown in Table 1. (P. 43). No new matter has been added.

The claims have been amended and new claims added to more particularly point out and distinctly claim the subject matter Applicants regard as their invention.

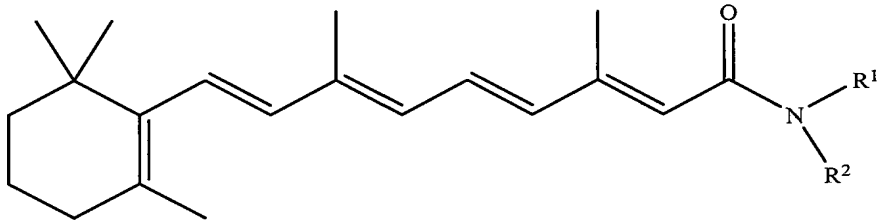
Claims 11, 19 and 20 stand rejected as indicated on pp. 2-3 of the Office Action. At ¶8 of the Office Action Summary, it is indicated that claims 11, 19 and 20 were subject to a restriction requirement and/or election requirement. Since the Office Action does not set forth any new such requirement, Applicants believe that claims 11, 19 and 20 were erroneously listed in ¶8, and that said claims should have been listed in ¶6 of the Office Action Summary as being rejected. Correction and clarification is respectfully requested.

Claim 21 stands withdrawn from consideration. As stated in the Listing of Claims section herein above, claim 21 should not be withdrawn because it depends from claim 20, which is not withdrawn, and because claim 21 merely adds an additional step. The compounds administered are still within the elected specie. Reconsideration and correction is respectfully requested.

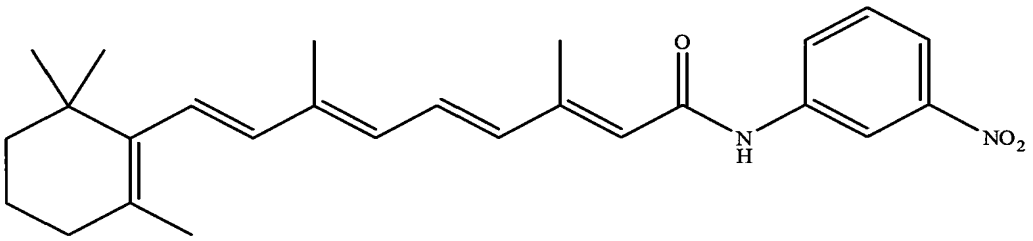
At pp. 2-3 of the Office Action dated September 19, 2007, claim 11 remains rejected under 35 U.S.C. § 103(a) as being unpatentable over Chem. Abst. 130:232097 to Clifford et al. (CA'097) or Chem. Abst. 134:65874 to D'Ambrosio et al. (CA'874) in view of DE 2,300,107 to Konig et al. Regarding DE 2,300,107, reference herein by Applicants is made to the English language equivalent embodied in GB Patent Specification 1,449,027 (GB'027). Regarding CA'874, reference herein by Applicants is made to the full journal article, D'Ambrosio SM et al., Differential Response of Normal, Premalignant and Malignant Human

Oral Epithelial Cells to Growth Inhibition by Chemopreventative Agents, *Anticancer Research* 20:2273-2280 (2000). ("D'Ambrosio"). Regarding CA'097, reference herein by Applicants is made to the full journal article, Clifford JL et al., Retinoid Receptor-dependent and -independent Effects of N-(4-Hydroxyphenyl)retinamide in F9 Embryonal Carcinoma Cells, *Cancer Research* 59, 14-18 (January 1, 1999). ("Clifford"). Applicants respectfully traverse the rejection.

GB'027 discloses "general formula I" being



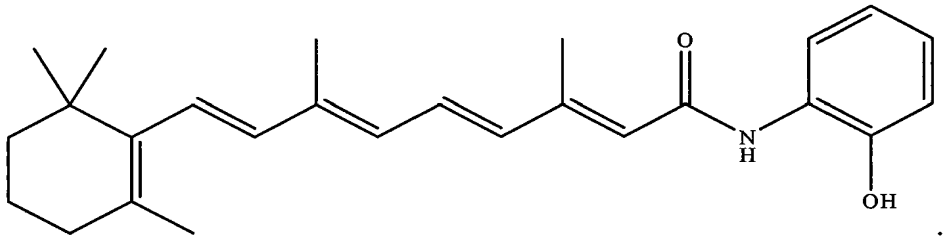
"in which R^1 is hydrogen" and R^2 may be "phenyl substituted by ... nitro." (P. 1, lines 13-30). In particular, GB'027 discloses "Vitamin A acid m-nitroanilide", which has the structure



(P. 7, line 50). GB'027 fails to disclose a hydroxy-substituted phenyl moiety. The compounds have use in treating "precanceroses and carcinomas." (P. 2, line 39).

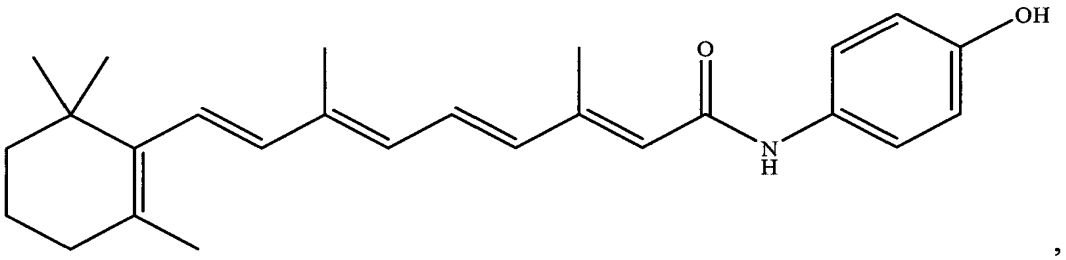
D'Ambrosio discloses various mono-hydroxy substituted phenyl retinamides:

N-(2-hydroxyphenyl)retinamide (2HPR) which has the structure



(See p. 2274, first column). GB'027 discloses that 2HPR "exhibited moderately effective GI [Growth Inhibition] values (~3) in the premalignant cell line." (P. 2275, col. 1) 2HPR "stimulated growth of the normal oral cells." (P. 2277, col. 1).

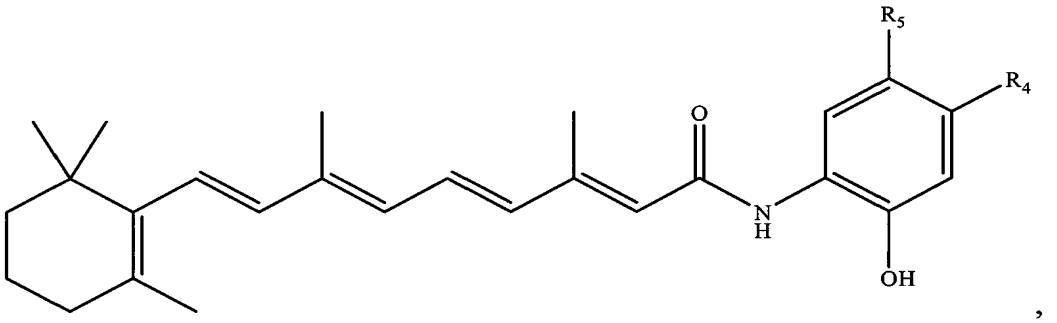
Clifford discloses that 4HPR,



,

has antitumor and chemopreventative activity. (See Abstract).

In contrast to the compounds and structures disclosed in GB'027, D'Ambrosio and Clifford, instant claim 11 is directed to an arylretinamide compound containing a di-substituted 2-hydroxy aryl moiety "according to the structure



,

wherein R_4 or R_5 is NO_2 and the other of R_4 or R_5 is H, or a pharmaceutically acceptable salt thereof." Instant compound 18 results from R_4=NO_2 and R_5=H, and compound 19 results from R_4=H and R_5=NO_2.

The instantly claimed invention is patentably nonobvious over Clifford, D'Ambrosio and GB'027. Clifford, D'Ambrosio and GB'027 fail (alone and collectively) to render the instantly claimed invention *prima facie* obvious under 35 USC § 103(a) because, *inter alia*, there is no implicit or explicit motivation to combine the references. Moreover, no motivation has been made of record.

Assuming the references are properly combinable, the comparative data shown at compounds 18 and 19 in Table 1 demonstrate unexpectedly superior (i.e., synergistic) growth inhibition activity as compared to 4HPR. Compounds 18 and 19 both demonstrated ">50% the activity" of 4HPR. (Table 1, fn. a). Greater than expected results are evidence of nonobviousness. (See MPEP 716.02(a)).

Furthermore, other comparative data in instant Table 1 demonstrate that NO_2 substitution at the instantly claimed 4 or 5 position is critical to achieving unexpectedly superior growth inhibition. NO_2 is substituted at the 2-position in compound 16. NO_2 is substituted at the 3-position in compound 17. Compounds 16 and 17 demonstrated "activity equivalent to vehicle." (Table 1, fn. a). Clearly, the instant comparative data is sufficiently probative of secondary considerations of nonobviousness to rebut any *prima facie* case of obviousness should one exist.

The examiner's conclusory assertion that "[a]pplicants' specification does not show superior results for compound 18, but merely shows greater than half of the activity of the 4-HPR standard" is not well taken. (Office Action at p. 3). Applicants respectfully submit that the relevant chemical/biological technology is unpredictable, and that the >50% increase in growth inhibition of cultured MCF-7 cells achieved by compounds 18 and 19 is compelling evidence of nonobviousness.

For the foregoing reasons, Applicants respectfully submit that the instantly claimed invention is patentably nonobvious over prior art of record, and Applicants request reconsideration and withdrawal of the obviousness rejections.

At pp. 2-3 of the Office Action, claims 19 and 20 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Clifford or D'Ambrosio in view of GB'027. Claim 19 is directed to a method of inducing apoptosis in human breast cancer cells using the compounds of claim 11. Claim 20 is directed to a method of treating human breast cancer also using the compounds of claim 11. Applicants respectfully traverse the rejection.

The compounds of claim 11 are novel over the prior art of record. The compounds of claim 11 are also nonobvious over the prior art of record for the reasons set forth above. Moreover, none of the cited references teach or suggest inducing apoptosis in human breast cancer cells or treating human breast cancer.

Clearly, claims 19 and 20 are patentably nonobvious over Clifford, D'Ambrosio and/or GB'027. Reconsideration and withdrawal of the rejection is respectfully requested.

At p. 3 of the Office Action, claims 19 and 20 are rejected under 35 U.S.C. § 112, First Paragraph as being nonenabled. Applicants respectfully traverse the rejection.

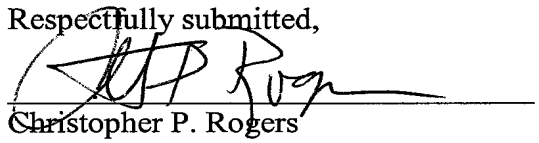
The claims have been amended to cover compounds 18 and 19 (and pharmaceutically acceptable salts), which (as discussed above) have unexpectedly superior growth inhibition

activity of MCF-7 cells. Reconsideration and withdrawal of the rejection is respectfully requested.

In view of the remarks made herein, Applicants respectfully request reconsideration of claims 11 and 19-23 and that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fees under 37 CFR § 1.17 that may be due on this application to Deposit Account 17-0055. The Commissioner is also authorized to treat this amendment and any future reply in this matter requiring a petition for an extension of time as incorporating a petition for extension of time for the appropriate length of time as provided by 37 CFR § 136(a)(3).

Respectfully submitted,



Christopher P. Rogers
Reg. No. 36,334
Attorney for Applicants
QUARLES & BRADY LLP
P.O. Box 2113
Madison, WI 53701-2113

TEL (608) 251-5000
FAX (608) 251-9166